Decision Memo for Positron Emission Tomography (FDG) for Thyroid Cancer (CAG-00095N)

Decision Summary

CMS determines that the evidence is not adequate to conclude that the use of FDG PET for the initial staging of post-surgical thyroid cancer of cell types that are known to concentrate I-131 poorly is reasonable and necessary for the diagnosis or treatment of the illness or injury or to improve the functioning of a malformed body member in the population specified in the request for national coverage.

CMS determines that the evidence is adequate to conclude that the use of FDG PET for staging of thyroid cancer of follicular cell origin previously treated by thyroidectomy and radioiodine ablation with an elevated or rising serum Tg > 10 ng/ml and negative I-131 WBS is reasonable and necessary for the diagnosis or treatment of the illness or injury or to improve the functioning of a malformed body member in the population specified.

CMS determines that the evidence is not adequate to conclude that the use of FDG PET for re-staging of previously treated thyroid cancer of medullary cell origin with an elevated serum calcitonin and negative standard imaging tests is reasonable and necessary for the treatment or diagnosis of the illness or injury or to improve the functioning of a malformed body member in the population specified in the request for national coverage.

CMS determines that the use of FDG PET for identifying patients with metastatic thyroid cancer who are at highest risk for death over the following three years is for informational purposes only and not for changing patient management, and, therefore, is not reasonable and necessary for the diagnosis or treatment of the illness or injury or to improve the functioning of a malformed body member in the population specified in the request for national coverage.

Other uses of FDG PET for thyroid cancer were not addressed and remain noncovered.

Therefore, we intend to issue a national coverage determination announcing these decisions.

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Decision Memo

This decision memorandum does not constitute a national coverage determination (NCD). It states CMS's intent to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction giving specific directions to our claims-processing contractors. That manual issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare Coverage Issues Manual. Policy changes become effective as of the date listed in the transmittal that announces the Coverage Issues Manual revision.

TO: Administrative File CAG: #00095N
FDG Positron Emission Tomography (PET) for Thyroid Cancer

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SUBJECT: National Coverage Determination for FDG PET for Thyroid Cancer
DATE: April 16, 2003

This memorandum serves three purposes: (1) provides background for this coverage decision, (2) analyzes relevant scientific and clinical literature related to the use of FDG PET scans in managing thyroid cancer, and (3) delineates the reasons for and announces our national coverage determination (NCD).

Clinical Background

Although thyroid nodules are extremely common, thyroid cancer is relatively rare. Clinically recognized thyroid cancers constitute less than 1 per cent of all human malignant tumors. Thyroid cancer, however, is estimated to be as prevalent as multiple myeloma, twice as common as Hodgkin's disease, and comparable in frequency to cancers of the esophagus, larynx, mouth, and uterine cervix. The American Cancer Society estimates that in the year 2001 approximately 19,500 new cases of thyroid cancer were diagnosed in the United States and that approximately 1,300 thyroid cancer-related deaths occur annually. Still, with early detection and appropriate treatment, the survival rate from thyroid cancer is very high. It is estimated that in the United States there are over 190,000 thyroid cancer survivors, some living more than 40 years after diagnosis.

Typically, it is difficult to distinguish a benign from a malignant thyroid lump or nodule on the basis of a history and physical examination, even with the use of clinical laboratory tests and radioactive iodine or other nuclear medicine scans of the thyroid. The only certain method of determining whether a patient has thyroid cancer is by the use of a fine needle or surgical biopsy of the lump or nodule.

When thyroid cancer has been diagnosed for a particular patient, it is important to consider the type of thyroid cancer to determine the seriousness of the cancer and the available treatments. There are several classification systems for identifying the various types of thyroid cancer. For purposes of this decision memorandum, we will be using a classification system that groups thyroid cancers into categories that correspond to the two types of thyroid cells: (1) cancers of follicular cell origin, and (2) cancers of parafollicular or C cell origin, i.e., medullary cancer. This classification system is consistent with the medical indications proposed for Medicare coverage of the use of FDG PET in management of thyroid cancer by the American Thyroid Association (ATA). It also reflects the general categories of thyroid cancer discussed in the May/June 2001 American Association of Clinical Endocrinology/American Association of Endocrine Surgeons (AACE/AAES) Guidelines for the Management of Thyroid Cancer.

Four distinct histologic types of follicular cell-derived cancers are recognized. The majority of cases are papillary and are typically well differentiated. The other histologic types include follicular, oxyphilic or Hürthle cell, and anaplastic. Each tumor type is believed to differ from the other tumor types relative to the initial mode of spread and subsequent pattern of recurrence and metastatic involvement.

Treatment of thyroid cancer depends on the type and stage of the thyroid disease, as well as the age and overall health of the patient. Treatments may include surgery, radioactive iodine (I-131) therapy, thyroid hormone therapy, and external beam radiation therapy. Surgery is the most common form of treatment for thyroid cancer of all types that have not spread to distant parts of the body. The surgeon usually removes part or, more commonly, all of the thyroid (thyroidectomy) and any other affected tissue, such as lymph nodes. After surgery, patients may be treated with radioactive iodine therapy and this treatment may be repeated at a later time. Thyroid hormone is also given as replacement therapy following surgery or radioactive iodine therapy and as suppressive therapy to slow the growth of any remaining thyroid cancer cells in patients with cancers of follicular cell origin.

Several clinical laboratory tests and nuclear imaging tests are available to clinicians to determine whether there has been local recurrence or metastasis of the thyroid cancer. In follicular cell-derived cancer, the detection of persistent or recurrent thyroid cancer relies on the unique ability of most cancers of this type to concentrate radioactive iodine and secrete a thyroid specific tumor marker known as thyroglobulin (Tg). Radioactive iodine scanning detects and localizes persistent or recurrent differentiated thyroid cancer in many, but not all patients with known metastatic disease. In the vast majority of the remaining cases, the presence of metastatic disease is evidenced by an elevated or rising serum Tg level. But an elevated Tg level simply documents the presence of persistent thyroid disease without localizing the lesion for treatment purposes. Despite the availability of a wide variety of imaging techniques, identifying the source of an elevated or rising serum Tg when the radioactive iodine scan is negative continues to be a significant management challenge.

Similarly, in the case of medullary cancer, residual or recurrent disease can be detected by specific biochemical markers - calcitonin or carcinoembryonic antigen. Management is difficult when routine imaging studies for medullary cancer such as somatostatin receptor scintigraphy (SRS), computed tomography (CT), and magnetic resonance imaging (MRI) are negative in the face of elevated calcitonin or elevated carcinoembryonic antigen tumor marker.

FDG PET scanning has been proposed as one possible test for resolving this difficulty in determining the presence and location of these two types of residual or recurrent metastatic thyroid cancer.

Description of FDG PET

FDG PET is a diagnostic imaging procedure that assesses the level of cellular glucose metabolism in various organ systems of the human body. Images are obtained from positron-emitting radioactive tracer substances (radiopharmaceuticals) administered intravenously to the patient. FDG PET has been evaluated for several decades in pre-clinical models, and is premised on basic research in biochemisty and biology that has established the basis of glucose metabolism in normal cell function, as well as it's alteration in diseases like cancer. As a molecular diagnostic imaging modality, FDG PET detects differences in metabolic activity, whereas anatomical imaging modalities such as x-ray films, CT and MRI depend on the size and radiographic characteristics of lesions to determine the likelihood of malignancy. FDG PET may detect metabolic abnormalities when anatomic imaging studies are negative and FDG PET may be informative in differentiating benign from malignant processes. In addition, whole body imaging with FDG PET can examine all organ systems for recurrent or metastatic disease in a single procedure.

Food and Drug Administration (FDA) Status

The FDA approval letter for new drug application NDA 20-306, dated June 2, 2000 included the following language:

"This new drug application provides for the use of Fluorodeoxyglucose F-18 injection for the following indications:

Assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.... We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter....[1]"

Benefit Category

In the preamble to a final rule dated November 1, 2002, CMS noted:

" Section 1861(t)(1) provides that the terms drugs and biologicals ``include only such drugs (including contrast agents) and biologicals, respectively, as are included (or approved for inclusion) in [one of several pharmacopoeias] (except for any drugs and biologicals unfavorably evaluated therein), or as are approved by the pharmacy and drug therapeutics committee (or equivalent committee) of the medical staff of the hospital furnishing such drugs and biologicals for use in such hospital." A careful reading of this statutory language convinces us that inclusion of an item in, for example, the USPDI ... does not necessarily mean that the item is a drug or biological. Inclusion in such reference (or approval by a hospital committee) is a necessary condition for us to call a product a drug or biological, but it is not enough. Rather, if we are to call a product a drug or a biological for our purposes, CMS must still make its own determination that the product is a drug or biological....

The appropriate benefit category for all diagnostic radiopharmaceuticals...is 1861(s)(3). We will consider neither diagnostic nor therapeutic radiopharmaceuticals to be drugs as described in section 1861(t)."[2]

History of Medicare's Coverage of FDG PET for Thyroid Cancer and Timeline of Recent Activities

In the decision memorandum of December 15, 2000 (#CAG-00065N) regarding broad coverage for FDG PET, the Centers for Medicare & Medicaid Services (CMS) covered FDG PET for head and neck cancers, but specifically excluded thyroid cancer.

The American Thyroid Association (ATA) requested that we revisit this issue of using FDG PET for the management of thyroid cancer. To support its request for reconsideration, the ATA included literature that was not available at the time of the earlier decision. The ATA specifically requested that CMS reconsider coverage of FDG PET for thyroid cancer for the following clinical situations:

1. Localization of thyroid cancer that fails to concentrate sufficient radioactive iodine (RAI) to allow for reliable whole body radioactive iodine scan.

   1.1 Initial staging of thyroid cancers known to concentrate RAI poorly (such as Hürthle cell thyroid cancer, histological variants of thyroid cancer such as tall-cell or insular subtypes, and other poorly differentiated thyroid cancers.)

   1.2 Detection of persistent or recurrent thyroid cancer detected by an elevated serum thyroglobulin in which standard imaging studies have failed to identify the location of the metastatic lesions.

2. Localization of medullary thyroid cancer in patients with elevated calcitonin in which other imaging modalities fail to localize metastatic foci.

June 13, 2001	Request for reconsideration from the ATA was accepted. The proposed indications are described below: 1. Initial staging (post-surgical) of thyroid cancer of histological subtypes that are known to concentrate I-131 poorly (e.g., Hürthle cell & variants of papillary cancer such as tall cell and insular), and, thus, may not allow for reliable whole body iodine-131 scans. 2. Re-staging of recurrent or residual thyroid cancer of follicular cell origin in patients with elevated serum thyroglobulin levels, where standard imaging tests have failed to localize metastatic origins. 3. Re-staging of recurrent or residual thyroid cancer in patients with elevated serum calcitonin, where standard imaging tests have failed to localize metastatic lesions. 4. Identifying (prognosis on) patients with metastatic thyroid cancer of follicular cell origin at highest risk of death over the following three years.
July 5, 2001	CMS received letter from ATA clarifying some histological and pathological questions about the various forms of thyroid cancer.

Sept 10, 2001	CMS referred the topic to the Agency for Healthcare Research & Quality (AHRQ) for a technology assessment.
Oct 25, 2001	CMS received support for the request from the Society for Nuclear Medicine. The letter included a copy of a recent article not originally provided by the ATA.
April 15, 2002	CMS received and posted the final technology assessment on the CMS website.
Sept 25, 2002	MCAC met to discuss assessing evidence for diseases that affect small populations.

Summary of Evidence

Technology Assessment

A "Systematic Review of Positron Emission Tomography for Follow-Up of Treated Thyroid Cancer", by Ethan Balk, MD, MPH and Joseph Lau, MD of the New England Medical Center (NEMC) Evidence-Based Practice Center (EPC), under contract to AHRQ, focused on three questions of interest:

1. ***What is the test performance of FDG PET for localization or staging of previously treated thyroid cancer suspected to be metastatic for which standard imaging modalities have failed to localize metastatic lesions or are thought not to be helpful to locate metastatic disease?***
2. ***In the same population, what is the evidence that FDG PET affects health outcomes or alters management?***
3. ***What is the test performance and effect on clinical management of FDG PET for initial, pre-treatment, staging of patients with differentiated thyroid cancer types that commonly do not take up radioiodine?***

As stated in 42 CFR § 410.32, a diagnostic test is not reasonable and necessary unless its results are used by the treating physician (who also orders the test) in the management of the beneficiary's specific medical problem. The requestor's fourth question requested coverage of FDG PET in clinical situations in which the results would not be used for patient management. Therefore, it is not reasonable and necessary and was not addressed in this decision memorandum.

The complete TA, including all references and evidence tables, is available online via a hyperlink on the CMS tracking sheet.

Methods

The TA performed a systematic literature search to identify relevant articles on FDG PET scans and thyroid cancer. The search included the 27 articles submitted by the requestor and was also supplemented by articles in reference lists of relevant articles and reviews. The literature search yielded 1,392 citations. Of these, 41 reported data on FDG PET and treated thyroid cancer. To be considered for inclusion in the assessment, the studies had to report on the diagnostic performance of FDG PET or clinical outcomes of subjects who had a FDG PET, and had to include at least 10 subjects. An exception was that studies of medullary and other rare thyroid tumors were included regardless of sample size due to the scarcity of larger studies. Twenty-two studies did not meet the inclusion criteria. The remaining 19 studies reported data on treated thyroid cancer with an elevated marker and negative initial imaging test.

Summary of TA Conclusions

Overall, studies on the use of FDG PET for thyroid cancer are small. Two studies were prospective in design and included only subjects with biochemical evidence of metastasis and negative imaging tests. Only one allowed reliable estimates of test performance. Most other studies were retrospective case series. In addition, most studies included mixed populations of subjects with different disease types and different underlying likelihood of metastatic disease.

Blinding of FDG PET interpreters to clinical data was clearly apparent in five studies. Unblinded studies are less reliable since the interpretation of the FDG PET scan may in part be based on other clinical data.

Reference standards (the definition of whether a subject truly has or does not have metastatic disease) were not always well defined. All studies (except one with no data) used histology from biopsy or surgery to diagnose at least some subjects with positive FDG PET. Some studies also used histology to confirm the diagnosis in subjects with negative FDG PET. However, most subjects with a negative FDG PET were followed clinically without a clear description of how final diagnoses were made. The duration of clinical follow-up was inconsistently reported but was up to 3 years in some studies.

1. ***What is the test performance of FDG PET for localization or staging of previously treated thyroid cancer suspected to be metastatic for which standard imaging modalities have failed to localize metastatic lesions or are thought not to be helpful to locate metastatic disease?***

Two studies, Grunwald (1999) and Helal (2001), reported on at least 10 subjects with and 10 subjects without metastatic disease. Grunwald (1999) is the larger study and the only study with a large number of subjects without metastatic disease. The study had several methodological flaws, including being a retrospective study that apparently combined previously reported patients from multiple centers, not having a predetermined definition of a reference standard (whether subjects actually have metastatic disease or not), not blinding FDG PET interpreters from clinical data, and not focusing on subjects with elevated Tg and negative iodine-131 whole body scintigraphy (WBS). The evaluation of subjects with biochemical markers of disease and no other evidence of metastasis is only a sub-group analysis of the whole data set.

Helal (2001) was of relatively better quality, being a prospective, blinded study with predetermined reference standards and FDG PET interpreter blinding that focused on subjects with treated differentiated thyroid cancer, elevated Tg and negative WBS. While the subjects were consecutively submitted to FDG PET evaluation at one center, it is unclear if the subjects represented a selected sample of subjects who had their primary treatment at various hospitals. The Helal study is relatively small with only 11 subjects without metastatic disease.

The Grunwald (1999) and Helal (2001) studies had sensitivity of 88% and 96%, and specificity of 100% and 73%. Small sample size limits their reliability and, as in all diagnostic technologies, improved test accuracy does not necessarily result in improvements in patient outcomes. Using the random effects model, several studies including the two larger Grunwald and Helal studies had a combined sensitivity of 84% (95% confidence interval 73%-91%) and a pooled specificity of 56% (95% confidence interval 27%-82%).

Only one study provided test performance data for more than a handful of subjects with Hürthle cell tumors. Grunwald (1999) analyzed 20 subjects with Hürthle cell tumors, but no data were provided about their Tg levels and 2 of the subjects had a positive WBS. FDG PET sensitivity to diagnose metastatic disease was 87% and specificity was 100%.

No study had sufficient subjects to estimate the test performance of FDG PET for patients with treated medullary cancer, elevated calcitonin and negative standard imaging tests. Among six studies, the largest included only 6 subjects. No study included more than 1 subject without metastatic disease. Three studies had no subjects without metastatic disease. Therefore, no individual study provides useful information about the test performance of FDG PET for medullary cancer.

2. ***What is the evidence that FDG PET affects health outcomes or clinical management of previously treated thyroid cancer suspected to be metastatic for which standard imaging modalities have failed to localize metastatic lesions or are thought not to be helpful to locate metastatic disease?***

None of the studies were specifically designed to determine the effect of FDG PET on clinical management or outcomes in patients with treated thyroid cancer. Data on the effect of FDG PET on patient management or clinical outcomes for patients with treated differentiated thyroid cancer, elevated Tg and negative WBS were reported in seven small studies with a combined total of 97 subjects. Overall, about 80% of subjects with positive FDG PET scans were reported to have further treatment (surgery, radioiodine ablation, or retinoic acid treatment) based on the FDG PET results. In four studies, one-third of subjects had reported cure of metastatic disease from a change in management based on FDG PET. However, one study had a mean follow-up duration of only 6 months and two studies did not provide data on follow-up duration.

Data on the effect of FDG PET on patient management or clinical outcomes for patients with treated medullary cancer and elevated calcitonin are limited. One study of 8 subjects with negative standard imaging tests reported that 2 of the subjects had curative surgery based on FDG PET, but no follow-up duration was reported. The only study of subjects with medullary cancer that included more than 10 subjects evaluated patients regardless of other imaging test results. The study found that 60% of 15 subjects with positive FDG PET had surgery based on FDG PET, but no data were reported on cure rate. In view of such small studies and the absence of pertinent outcomes analysis, the TA concluded that no reliable estimates of the effect of FDG PET on clinical management or outcomes of patients with treated medullary thyroid cancer have been published. Similarly, no useful data have been reported on the effect of FDG PET on clinical management or outcomes of patients with other forms of thyroid cancer.

3. ***What are the test performance and effect on clinical management of FDG PET for initial, pre-treatment, staging of patients with differentiated thyroid cancer types that commonly do not take up radioiodine?***

The TA did not address this topic because of insufficient evidence. Only one study that met the technology assessment's inclusion criteria focused on the pretreatment population. This study reported on only 1 subject with Hürthle cell cancer.

Medicare Coverage Advisory Committee (MCAC) Executive Committee

On September 25, 2002, the MCAC Executive Committee met to discuss assessing evidence for diseases that affect small populations such as those in this request. Minutes and complete transcripts from the meeting are available on our website. The MCAC recommended that, even for diseases that affect small populations of patients, Medicare coverage should still be based on solid, scientific evidence.

Additional Articles

Because the TA excluded all meta-analyses, CMS extended its independent review of evidence to include a large meta-analysis by Hooft et al (2001). This report used eight internal validity criteria and ranked articles by their level of evidence. In this meta-analysis, studies were included if they were prospective or retrospective, had 10 human subjects or more, and evaluated the accuracy of FDG PET in patients suspected of recurrent follicular and papillary thyroid cancer. Initial attempts to carry out a quantitative meta-analysis found most studies had insufficient data to allow statistical pooling and the spectrum of patients was considered to be too heterogeneous. Subsequently, qualitative analysis regarding the value of FDG PET was based on the strength of the scientific literature according to the criteria for diagnostic tests recommended by the Cochrane Methods Group on Screening and Diagnostic Tests.

Fourteen studies met the inclusion criteria. Methodological problems included poor validity of reference tests and lack of blinding of test performance and interpretation. The most consistent data were found for FDG PET in evaluating patients with elevated serum Tg and negative iodine-131 WBS. All studies claimed a positive role for FDG PET at evidence levels 3 or 4 (1 = highest level; 4 = lowest level), but the reported high yield of FDG PET for localizing recurrent disease was noted to apply only to the included spectrum of patients with high serum markers indicative of recurrent disease. Serum marker levels and tumor load were positively related and the findings were unable to be extrapolated to patients with lower serum markers. Hooft's discussion also stated that the impact of altered therapy decisions on patient outcomes in both curative and palliative settings was not yet evident.

AACE/AAES Medical/Surgical Guidelines for Clinical Practice: Management of Thyroid Carcinoma (2001)

A set of clinical guidelines was produced by the American Association of Clinical Endocrinology (AACE), the American College of Endocrinology (ACE) and the American Association of Endocrine Surgeons (AAES). These updated thyroid cancer guidelines were developed by and represent a consensus of the Thyroid Carcinoma Task Force, consisting of 21 members of AACE and AAES, all of whom have contributed to current thyroid cancer clinical management strategies.

In "Table 3: Imaging Modalities Used in Follicular Cell-Derived Cancers", the guidelines indicate that the principal use for FDG PET is in patients whose WBS is negative and whose Tg level is high. The last column in the table also comments briefly on each type of imaging study and describes FDG PET as "probably [the] best nonspecific imaging modality; detects metabolically active, poorly differentiated disease."

Expert Opinion

In view of overall small sample sizes and poor study quality, CMS also carefully considered the opinions of outside reviewers of the technology assessment (TA) and other experts in the field of thyroid disease. Three reviewers in particular, Richard Robbins, MD, Professor of Medicine at Memorial Sloan-Kettering Cancer Center and Cornell University; Monica Skarulis, MD, Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the NIH's thyroid cancer unit; and Arthur Lurvey, MD, Medicare Carrier Medical Director, generally supported the conclusion that although the evidence is limited, it favors the use of FDG PET in patients with follicular cell thyroid cancer who have an elevated serum Tg and a negative WBS.

These same experts, in evaluating the evidence for medullary thyroid cancer, did not consistently favor the use of FDG PET and noted that data are too small to draw any conclusions.

There were no other public comments.

CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." § 1862(a)(1)(A).

CMS has issued regulations pertaining to the coverage of diagnostic tests under the Part B program. Those rules provide that, except for a few exceptions, diagnostic tests must be ordered by the physician who treats the beneficiary for a specific medical problem and the physician must use the results in the management of the beneficiary's specific medical problem (42 C.F.R. § 410.32). In general, tests not ordered by the physician who is treating the beneficiary are not reasonable and necessary. See also 42 C.F.R. § 411.15(k)(1).

CMS staff reviewed the literature included in the technology assessment as well as selected literature that did not meet the assessment's inclusion criteria. In this analysis, CMS focuses on the indications requested by the ATA.

Overall, most studies had small sample sizes which made valid statistical inferences difficult. Only two studies of differentiated thyroid cancer had sufficient sample sizes for reliable estimates of both sensitivity and specificity. For studies of medullary cancer, no study had at least 10 subjects who met the technology assessment's criteria. Studies that reported on rarer tumors were also too small to provide reliable estimates of test performance.

1. ***Initial staging (post surgical) of thyroid cancer of histological subtypes that are known to concentrate I-131 poorly (e.g., Hürthle cell & variants of papillary cancer such as tall cell and insular), and, thus, may not allow for reliable whole body iodine-131 scans.***

Insufficient data exist to estimate the test performance of FDG PET for the initial staging of thyroid cancers prior to definitive treatment with I-131 ablation. In addition, we were unable to locate any guidelines and there was no consistent expert opinion on the utility of FDG PET for this indication.

2. ***Re-staging of recurrent or residual thyroid cancer of follicular cell origin in patients with elevated serum thyroglobulin levels, where standard imaging tests have failed to localize metastatic origins.***

After reviewing the TA and our literature review, CMS was unable to find studies of sufficient quality in design and sample size to define the diagnostic characteristics of FDG PET in identifying metastatic disease in patients with treated differentiated thyroid cancer of follicular cell origin, elevated Tg and negative I-131 WBS. However, though studies on the effects of FDG PET in altering clinical management were also not optimal, they did demonstrate definite trends in prompting providers to modify therapy and, in a few studies, reported cure. In addition, guidelines from AACE/AAES, though not critically appraising the evidence, do support the use of FDG PET for this indication, as do the experts we polled. In addition, in this group of patients with elevated tumor markers and negative standard imaging tests, there are no other options for identifying disease.

Almost all studies reviewed by either the TA or by CMS included patients with serum Tg levels well above 10 ng/ml and there was inconsistency in measurement due to variable degrees of thyroid hormone withdrawal and TSH stimulation prior to testing. The large Hooft et al (2001) meta-analysis noted that the reported high yield of FDG PET in localizing recurrent disease in this subset of thyroid cancer patients applies to the included spectrum of patients with high serum Tg and cannot be extrapolated to situations with lower serum Tg. Schlüter et al (2001) also stratified FDG PET results by serum Tg level and concluded that true-positive FDG PET findings were correlated positively with increasing Tg levels. In their study, FDG PET was true positive in only 11% of patients with Tg <10 ng/ml, versus 50% with Tg between 10-20 ng/ml, and 93% with Tg >100 ng/ml.

Therefore, CMS concludes that, as discussed above, the totality of the evidence is adequate to support the clinical utility of FDG PET for restaging of recurrent or residual thyroid cancer of follicular cell origin in patients with serum thyroglobulin levels above 10 ng/ml, where standard imaging tests have failed to localize metastatic or recurrent disease.

3. ***Re-staging of recurrent or residual medullary thyroid cancer in patients with elevated serum calcitonin, where standard imaging tests have failed to localize metastatic lesions.***

Insufficient data exist to estimate the test performance or the impact on clinical management of FDG PET for treated medullary thyroid cancer and other rarer forms of thyroid cancer. The data is also insufficient to detect any trends or make any statistical inferences regarding the utility of FDG PET for this indication. In addition, there are no clinical guidelines or consistent expert opinion supporting this indication

4. ***Identifying (prognosis on) patients with metastatic thyroid cancer of follicular cell origin at highest risk of death over the following three years.***

As stated in 42 CFR § 410.32, a diagnostic test is not reasonable and necessary unless its results are used by the treating physician (who also orders the test) in the management of the beneficiary's specific medical problem. This question requests coverage of FDG PET in clinical situations in which the results would not be used for patient management. Therefore, it is not reasonable and necessary and was not addressed in this decision memorandum.

Decision

CMS determines that the evidence is not adequate to conclude that the use of FDG PET for the initial staging of post-surgical thyroid cancer of cell types that are known to concentrate I-131 poorly is reasonable and necessary for the diagnosis or treatment of the illness or injury or to improve the functioning of a malformed body member in the population specified in the request for national coverage.

CMS determines that the evidence is adequate to conclude that the use of FDG PET for staging of thyroid cancer of follicular cell origin previously treated by thyroidectomy and radioiodine ablation with an elevated or rising serum Tg > 10 ng/ml and negative I-131 WBS is reasonable and necessary for the diagnosis or treatment of the illness or injury or to improve the functioning of a malformed body member in the population specified.

CMS determines that the evidence is not adequate to conclude that the use of FDG PET for re-staging of previously treated thyroid cancer of medullary cell origin with an elevated serum calcitonin and negative standard imaging tests is reasonable and necessary for the treatment or diagnosis of the illness or injury or to improve the functioning of a malformed body member in the population specified in the request for national coverage.

CMS determines that the use of FDG PET for identifying patients with metastatic thyroid cancer who are at highest risk for death over the following three years is for informational purposes only and not for changing patient management, and, therefore, is not reasonable and necessary for the diagnosis or treatment of the illness or injury or to improve the functioning of a malformed body member in the population specified in the request for national coverage.

Other uses of FDG PET for thyroid cancer were not addressed and remain noncovered.

Therefore, we intend to issue a national coverage determination announcing these decisions.

Appendix

Technology Assessment (TA) submitted to AHRQ by the New England Medical Center EPC, Ethan Balk, MD, MPH and Joseph Lau, MD, Contract No. 270-97-0019, April 10, 2002. The complete TA, including all references and evidence tables, is available online via a hyperlink on the CMS tracking sheet.

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